

EuReCa International PhD Program
PhD thesis project
2020 Call for application



Mechanism of Caveolin-assisted transport and enrichment of sphingomyelin in the plasma membrane

General information

Call	2020
Reference	2020-01-BASSEREAU
Keyword(s)	Sphingomyelin traffic; caveolae; biomimetic membrane systems; membrane curvature; membrane asymmetry

Director(s) and team

Thesis director(s)	Patricia Bassereau & Christophe Lamaze
Research team	Membranes & Cellular Functions
Research department	UMR 168 – Physico-Chimie Curie Lab

Description of the PhD thesis project

How cells maintain strong differences in lipid composition among their compartments despite constant intracellular membrane exchanges by transport carriers remains mysterious. Thus, there is a 5-fold enrichment in sphingomyelin (SM) in the plasma membrane (PM) as compared to the trans-Golgi network (TGN) where SM is synthesized. SM enrichment in transport carriers cannot be explained by a bending energy minimization-based mechanism of lipid sorting, since SM form stiff membranes. We had hypothesized that protein-assisted lipid sorting could explain SM enrichment in transport carriers.

Indeed, we recently found that caveolin-depleted cells have lower SM levels in their PM. The membrane proteins Caveolins traffic from TGN to PM, which suggests that they could enrich SM at the PM, by assisting their inclusion in transport vesicles at the TGN. Caveolins are the structural components of small PM invaginations, called caveolae, rich in SM and cholesterol, that are involved in lipid homeostasis, mechanosensing and cellular signaling. How caveolins assist in SM recruitment is unclear, since caveolins are inserted like hairpins in the inner leaflet of the PM, whereas SM is in the outer leaflet.

The PhD objective is to uncover the physical mechanism of SM sorting by caveolin in asymmetric membranes. The student will develop novel in vitro reconstituted systems based on Giant Unilamellar Vesicles (GUV), and purified caveolin. S/he will study how caveolin influences SM sorting in curved membranes using quantitative fluorescence microscopy and the nanotube pulling assay with optical tweezers we established.

Caveolin reconstitution in GUV is already operational but so far only in membranes with symmetric leaflets. A challenge will be to prepare GUVs with asymmetric leaflets, mimicking the PM and to reconstitute caveolin in the opposite leaflet of SM-cholesterol. The new tools and physical models of this project will unravel protein-assisted lipid transport by caveolin and beyond.

International, interdisciplinary & intersectoral aspects of the project

The thesis will be co-supervised by P. Bassereau (Biophysicist) and C. Lamaze (Cell biologist). The project has already started with a joint post-doc (J. Podkalicka), biochemist and biologist working on the in vivo aspects, who will directly interact with the PhD.

For reconstitution, the Bassereau group collaborates closely with D. Lévy and M. Dezzi, structural biologists that are experts in membrane proteins. We collaborate with A. Kenworthy (Virginia Univ.), who studies caveolin structure and C. Burd (Yale Univ.) who develops SM markers.

A scientist of the L'Oréal company will participate to the thesis committee and the student will have the possibility to interact with the L'Oréal advanced microscopy platform. Finally, the thesis will have the "Doctor Europaeus" label.

Recent publications

1. Pernier J., Kusters R., Bousquet H., Lagny T., Morchain A., Joanny J.-F., **Bassereau P.***, Coudrier E.* Myosin 1b is an actin depolymerase Nat. Commun. (2019) 10 5200. doi: 10.1038/s41467-019-13160-y.
2. Tsai F.-C., Bertin A., Bousquet H., Manzi J., Senju Y., Tsai M.-C., Picas L., Miserey-Lenkei S., Lappalainen P., Lemichez E., Coudrier E.*, **Bassereau P.*** Ezrin enrichment on curved cell membranes requires phosphorylation or interaction with a curvature-sensitive partner eLife (2018) 7 e37262. doi:10.7554/eLife.37262.
3. Simunovic M., Manneville J.-B., Renard H.-F., Evergren E., Raghunathan K., Bathia D., Kenworthy A. K., Voth G. A., Prost J., McMahon H., Johannes L., **Bassereau P.***, Callan-Jones A.* Friction Mediates Scission of Tubular Membranes Scaffolded by BAR Proteins Cell (2017) 170 172-184. doi: 10.1016/j.cell.2017.05.047
4. Torrino S, **Lamaze C.** EHD2 is a mechanotransducer connecting caveolae dynamics with gene transcription. J Cell Biol. (2018) 217 4092-4105. doi: 10.1083/jcb.201801122
5. Blouin CM, **Lamaze C.** Glycosylation-dependent IFN- γ R partitioning in lipid and actin nanodomains is critical for JAK activation. Cell (2016) 166 920-934. doi: 10.1016/j.cell.2016.07.003.

Expected profile of the candidate

Applicants should be interested to work in an interdisciplinary environment and to explore biological questions with physics tools and concepts. A background in soft matter physics or biophysics is recommended but not mandatory. The project highly relies on reconstituted systems and has strong relevance for cell biology questions, for which the applicant should either have experience or a strong motivation to learn.